EXHIBIT I

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ORIGINAL ARTICLE

Anatomical variability in the trajectory of the inside-out transobturator vaginal tape technique (TVT-O)

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Abstract An experimental surgical study on human cadavers was undertaken to assess variability in the trajectory followed by the needle during application of the inside-out transobturator tape suspension (TVT-O) technique. The TVT-O surgical procedures were performed on six fresh female cadavers according to the standard recommended operative protocol. Subsequent anatomical dissection revealed that the needle had perforated the obturator membrane at a distance of 0.7 to 2.0 cm from the needle to the obturator canal. It subsequently followed a variable course passing at 0.5 to 2.0 cm from the anterior branch of the obturator nerve and 0.1 to 1.4 cm from the posterior branch. We conclude from this anatomical study that the TVT-O trajectory is subject to wider variability than was originally postulated.

Keywords Urinary incontinence · Anatomy · Obturator nerve · TVT-O · Transobturator tape

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Introduction

The introduction of the mid-urethral sling as an ambulatory procedure by P. Petros and U. Ulmsten in 1995 [1] dramatically changed the management of urodynamic stress incontinence. Colposuspension, as the gold standard, seemed to be replaceable by a standardised, non-obstructive tape suspension that could be performed under local anaesthesia. With reported continence rates as high as 81% after 91 months and randomised controlled trial data demonstrating equal effectiveness, it is no surprise that the mid-urethral sling is becoming the preferred management option for the treatment of urodynamic stress incontinence [2, 3]. The tension-free vaginal tape (TVT) procedure is associated with an incidence of 6.3% bladder perforations and 1.7% mild vascular injuries [4]. In 2001, the transobturator approach for mid-urethral tape suspension was introduced as a means to steer clear of the retropubic space and, hence, to avoid bladder perforations and vascular injuries [5]. In 2003, J. de Leval [6] introduced yet another modification, the inside-out transobturator route (TVT-O), aiming at further reduction in the risk of bladder and urethral injury. The metal introducer shields the needle away from the urethra and guides its transobturator passage inferiolateral to the bladder. The use of the metal introducer allows for a minimal paraurethral dissection. This holds the theoretical advantage of less neuronal damage near the bladder neck and a more stable positioning of the suspensory tape.

From an anatomical study regarding this TVT-O procedure, Bonnet et al. [7] concluded that "the tape is inserted in a consistent path that is highly accurate, reproducible and safe, independent of surgeon experience". Other reported studies [8–10], whilst confirming overall good feasibility of the TVT-O technique, were indicative of a wider intra- and inter-study variability in the path followed by the needle.

Because the technique may well become the standard procedure for comparing newly developed instrumentation, and considering the self-evident rule that patient characteristics and operator skills are important factors determining variability in the needle path, we undertook the present study to establish baseline values for application of the technique in our local setting. To test the external validity of the anatomical study by Bonnet et al., the group who invented the TVT-O, we performed the technique on cadavers and assessed the variability in needle trajectory by subsequent anatomical dissections.

Materials and methods

TVT-O procedures and dissections on cadavers were performed at the department of Human Anatomy of the University of Hasselt. The cadavers had been stored at 4°C for a maximum of 48 h after decease. Before surgery, the cadavers were allowed to accommodate to room temperature for 2–3 h, which made conditions for tissue manipulation comparable to those encountered in live surgery. Five cadavers were operated upon while lying in the dorsal supine lithotomy position with the legs in abduction and at least 100° flexion of the hips. The sixth cadaver was operated upon with the legs slightly more in extension to illustrate the important effect of hip flexion on the needle's trajectory. Both surgeons (PH and SS) had extensive experience in applying the TVT-O procedure. The TVT-O was placed according to the methods described by de Leval [6]. To allow for assessment of inter-observer variability, each operator would alternately operate the left and, subsequently, the right side of the patient.

The dissections were undertaken by the anatomist (LV) after completion of the operative procedure. The skin was incised over the ischiopubic ramus and the medial border of the *m. adductor longus*. The triangular skin flap overlying the adductor region was then removed. The *m. adductor longus* and *m. gracilis* were dissected. The anterior branch of the obturator nerve, inside the plane between *the m. adductor longus* and *m. adductor brevis*, was identified. The posterior ramus of the obturator nerve was subsequently identified inside the plane between the *m. adductor brevis* and m. *adductor magnus*. These two (peripheral) branches of the obturator nerve were followed medially toward its stem emerging from the obturator canal. To visualise the obturator canal more clearly, the *m. gracilis*, *m. adductor longus* and *brevis* and the *m. obturator externus* were cut at their insertion on the ischiopubic ramus and reflected laterally.

The distances, in centimetres, were measured at different stages during the dissection to preserve the spatial relations between the muscles, nerves and vessels. The distances between the needle and the nerves relate to the shortest distance observed between them. The ischiopubic ramus was measured from the ischial tuberosity to the midpoint of the pubic symphysis. The midpoint of the ischiopubic ramus was determined and subsequently used as a reference for measuring the distance from the ischiopubic ramus to the needle. This measurement is indicative of the lateral course of the needle.

All steps were captured on digital film.

Results

A total of 12 trajectories of the TVT-O needle were dissected and studied. Table 1 lists all individual measurements. All measurements are reported, as this more clearly illustrates the inter- and intra-individual variability of the needle's trajectory. No distinct anatomic differences between the right and left hemipelvis were witnessed. Anatomical defects within the bony pelvis or past trauma to the cadaveric pelves were not present.

The needle passed, on average, 1.5 cm (range, 0.7–2.0 cm; median, 1.45 cm) inferior–medial to the obturator canal. The anterior branch of the obturator nerve was, on average, 1.6 cm (range, 0.5–2.0 cm; median, 1.7 cm) from the needle's path. The posterior branch of the obturator nerve was, on average, 0.7 cm (range, 0.1–1.2 cm; median, 0.9 cm) from the needle's path. The average distance from the midpoint of the ischiopubic ramus to the closest encounter of the needle at this point measured 2.4 cm (range, 1.9 to 3.5 cm; median, 2.3 cm). Figure 1a–f illustrates the dissection of the third cadaver.

Table 1 Individual measurements (in cm) from the needle to the relative structures in all five cadavers

Distance to needle (cm)	Cadaver 1		Cadaver 2		Cadaver 3		Cadaver 4		Cadaver 5		Median
	Left	Right	Left	Right	Left	Right	Left	Right	Left	Right	
Obturator canal	1.8	2.0	1.4	1.5	2.0	2.0	1.1	0.7	1.4	1.3	1.45
Anterior obturator nerve	1.8	2.0	1.7	1.7	0.5	1.5	2.0	2.0	1.5	1.5	1.7
Posterior obturator nerve	1.0	1.2	0.9	0.9	0.1	1.0	0.1	0.1	0.5	0.7	0.9
Midpoint ischiopubic ramus	2.3	2.4	2.1	2.0	2.5	2.0	3.5	3.0	2.1	1.9	2.3

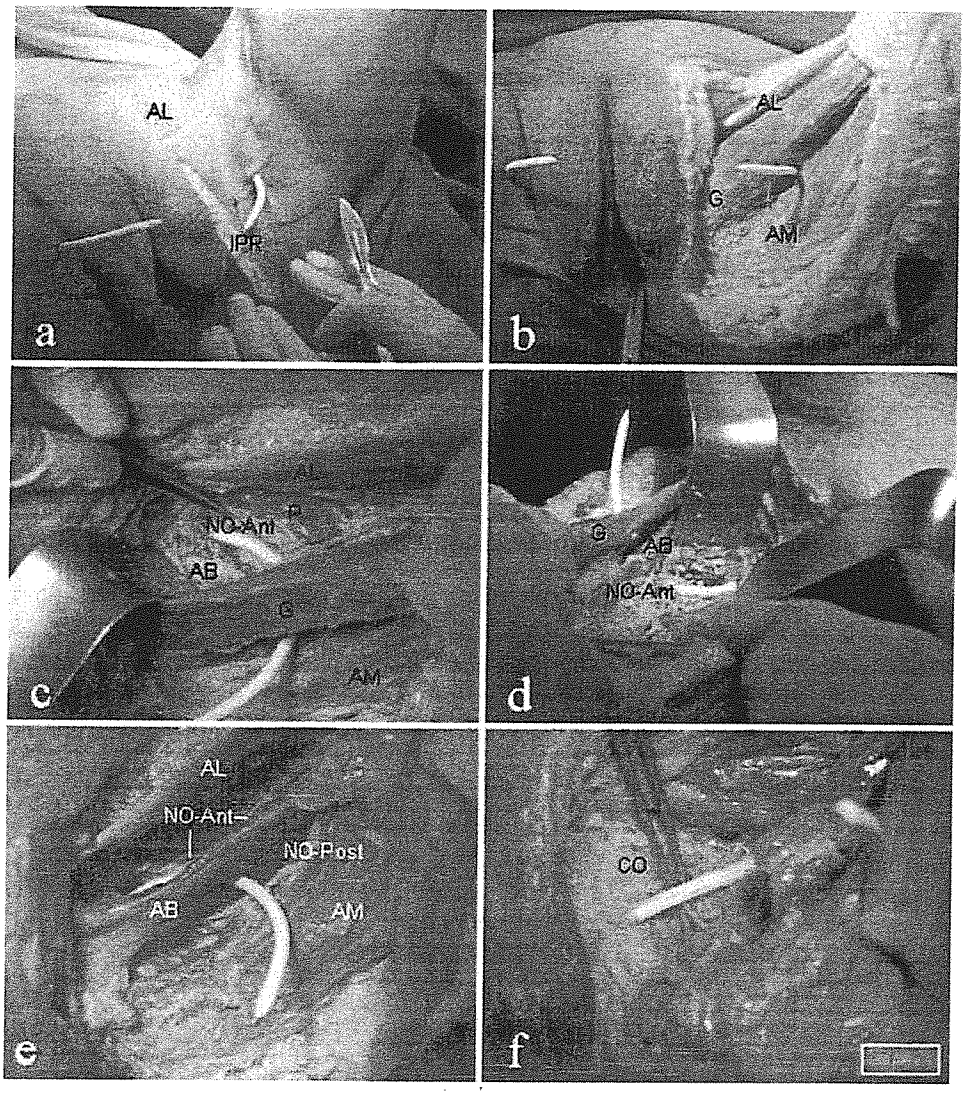

Fig. 1 Cadaver with legs in abduction, externally rotated and hyperflexed (*left side*). All pictures are a view in the lithotomy position, except **d** which is taken from a ventral position. *AL*, *m. adductor longus*; *AB*, *m. adductor brevis*; *AM*, *m. adductor magnus*; *OE*, *m. obturatorius externus*; *G*, *m. gracilis*; *P*, *m. pectineus*; *NO Ant*, *n. obturatorius ramus anterior*; *NO Post*, *N. obturatorius ramus posterior*. **a** TVT-O device in situ. Anatomical skin incision over ischiopubic ramus and the medial border of the *m. adductor longus*. **b** Superficial layer of the adductor muscles. **c** View of the anterior branches of the *n. obturatorius*, *m. gracilis* and *m. adductor brevis* reflected. **d** Ventral view also demonstrating the anterior branches of the obturator nerve. The anterior valve reflects the *m. gracilis* and *m. adductor brevis* which is perforated by the device. The index finger is on top of the *m. adductor longus*. **e** *M. gracilis* resected. View on the anterior branch of the obturator nerve and the posterior branch, both separated by the *m. adductor brevis* which is perforated by the needle. **f** *M. adductor brevis* resected, view of the obturator canal

Listed averages and medians do not include the sixth cadaver's data, as this specimen was purposefully operated upon in a position not conform the standard operating guidelines. The needle in the sixth cadaver, with the legs extended at approximately 80°, followed a far too cranial and lateral course compared to the average path encountered in the correctly positioned patient. The needle passed on 0.5 cm on both sides inferior–medial to the obturator canal. The anterior branch of the obturator nerve was 0.5 and 0 cm (left and right, respectively) from the needle's path. The posterior branch of the obturator nerve was 1.3 and 1.5 cm (left, right) from the needle's path. The distance from the midpoint of the ischiopubic ramus to the closest encounter of the needle in the malpositioned cadaver measured 4.2 and 4 cm (left and right respectively), indicative of the abnormal lateral deflection of the needle secondary to the malpositioning.

Discussion

The data presented in this anatomical study of the TVT-O procedure show variable measurements of the needle's trajectory in relation to the bony landmarks (ischiopubic ramus) and the neurovascular structures (obturator canal and obturator nerve ramus anterior and posterior). Table 2 compares our data to those of similar anatomical studies currently available in the literature.

Our data differ from the first original anatomical article on the TVT-O procedure by Bonnet et al. [7] who measured an average of 2.6 cm from the obturator canal in 13 cadavers (range 2.2–3.0 cm). Reisenauer et al. [8] also measured an average of 2.5 cm (range 2.0–2.9 cm) in five cadavers. This is significantly longer than the 1.5 cm (range 0.7–2 cm) found in the present study. Achtari et al. [9], operating on embalmed, not fresh cadavers, likewise

Table 2 Comparison of data with those of similar anatomical studies

Author	Whiteside and Walters [14]	Achtari et al. [9]		Bonnet et al. [7]	Reisenauer et al. [8]	Spinosa et al. [10]		Hinoul (present study)
Procedure	Monarc	Monarc	TVT-O	TVT-O	TVT-O	T.O.T.	TVT-O	TVT-O
Obt canal	2.3 (1.5–2.8)	2.7 (2.2–3.5)	1.9 (1.7–2.6)	2.6 (2.2–3.0)	2.5 (2.0–2.9)	–	–	1.5 (0.7–2.0)
Ant obt N	2.6 (1.5–4.5)							1.6 (0.5–2.0)
Post obt N	2.5 (1.2–3.5)	–	–	–	–	2.7 (2.1–3.3)	0.9 (0–1.2)	0.7 (0.1–1.2)

measured shorter distances to the obturator canal than Bonnet et al. [7]. Their average distance to the obturator canal of 1.9 cm (range 1.7–2.6 cm) is still significantly longer than our measurement. An even greater discrepancy was noted in the malpositioned cadaver (hip flexion of ca 80° instead of 100°) in which the distance between the obturator canal and the needle was as small as 0.5 cm. Correct (hyper)flexion causes a ventro-cranial tilting of the pelvis in relation to soft tissues at the point of entry of the needle and, hence, optimises its relation to the obturator canal and neurovascular bundle. This consideration implies that in cases where guidelines for correct patient positioning cannot be respected, the needle's trajectory will differ significantly from the originally described "consistent track independent of surgeon experience" as stated by Bonnet et al. [7].

The present study also reports on the measurements between the TVT-O needle passage relative to the course of the peripheral obturator nerve's branches. The distance to the anterior obturator nerve varied from 0.5 to 2.0 cm, and to the posterior obturator nerve from 0.1 to 1.2 cm. In a similar anatomical study involving seven TVT-O trajectories, Spinosa et al. [10] measured an average distance to the posterior obturator nerve of only 0.9 cm, with a range of 0 to 1.2 cm. Spinosa's and our data refute the statement by Reisenauer et al. [8] that "the distance between the tape and the posterior ramus of the obturator nerve is the same as the distance between the tape and the obturator canal". The smaller distance to the nerves found in our and Spinosa's study may be accounted for by several factors. First of all, they again illustrate the importance of hip flexion. The anterior and posterior branches of the obturator nerve are separated by the adductor brevis muscle. Hyperflexion, abduction and external rotation move the obturator nerves along the femoral axis, away from the tape's trajectory. The large variation in our measurements can be partially explained by the fact that all five cadavers were positioned in maximum flexion that could physically be achieved. This, however, resulted in a wider range of hyperflexion degrees varying from 100° to 110°. It is important to note that this variation is bound to occur in patients that are obese, have had hip surgery or suffer from severe arthrosis. The importance of hyperflexion in the hips is even more accentuated by our sixth cadaver's dissection in which the procedure was performed at only 80° flexion. The trajectory in this cadaver no longer ran below and medial to the obturator nerve, but curved above the posterior branch of the obturator nerve, and laterally reached, and even perforated its anterior branch. Considering that optimal flexion of the hips cannot always be achieved and taking into account the anatomy of the obturator nerve in relation to the bony pelvis, it is useful to contemplate that tilting the pelvis would achieve a similar deflection of the nerve's path, away from the horizontal trajectory of the TVT-O needle. Therefore, the effect of Trendelenburg positioning as a safety measure to avoid neural damage should be investigated further.

The second proposed explanation for the variation of the needle's peripheral trajectory is operator-dependent and is related to the insertion of the guide's tip. The incision of the vaginal wall should be 1 cm from the urethral meatus. Inadvertent insertion of the introducer closer to the bladder neck can lead to a shorter distance between the needle and the obturator canal. The metal guide should be sited precisely behind the ischiopubic branch. In case the guide is inserted more deeply, the needle will start its angulation slightly more laterally. Because the trajectory is that of a curved needle, even a small deviation at the insertion will cause an important deflection peripherally. Moreover, the point of insertion is also dictated by the shape and volume of the inferior ischiopubic arch. Although in a blind procedure it is difficult to exactly locate the edge of the inferior ischiopubic arch, a more robust arch will require a deeper insertion point to allow for the needle's angulation around it.

The third explanation for the needle's variable trajectory is also operator-dependent, as its path will be determined by the surgeon's manoeuvring of the needle's handle. Our findings demonstrate that it is important to bring the needle's handle from a 45° angle to a vertical position as early as can be achieved after perforating the obturator membrane, as this will force the needle into a more "horizontal" (i.e. less cranial) course. Moreover, the course of the needle's trajectory left and right of the cadavers was not always symmetrical, e.g. the difference in distances to the nerves

measured in cadaver 3. This indicates that the course is indeed determined not only by the patient's individual anatomy but also by intra- and inter-operator variation.

The dissections, furthermore, demonstrate that a more lateral passage of the needle reduces the distance to the nerve endings. This can be inferred from the distances from the needle to the midpoint of the ischiopubic ramus, which represent the lateral displacements of the needle. The left side of cadaver 3 and both sides of cadaver 4 show a significantly larger distance to the midpoint of the ischiopubic ramus (thus, a more lateral displacement of the needle) and consequently the shortest distance to the posterior branch of the obturator nerve (Table 1). As we measured a distance to the nerve of only 0.1 cm in three passages and one actual perforation of a nerve in the malpositioned patient, it seems prudent to design the insertion devices with a blunt tip as is the case in the TVT-O. Sharp needles will probably lead to more actual perforations of nerves and vessels. Slightly aberrant trajectories will unlikely result in a different objective cure rate for urodynamic stress incontinence, with cure rates being reported as high as 91% [12]. However, injury to the obturator nerve may lead to pain, paresthesia and partial loss of strength of some adductor muscles. The suspicion that the inside-out procedure is linked to more neurological injuries was already raised in de Leval's [6] original article in which 27 patients of the 107 who underwent the TVT-O procedure reported (moderate, temporary) pain in the thigh folds. A recent review of the data collected by the Manufacturer and User Facility Device Experience database also implies more pain, neuropathy and excessive bleeding in the inside-out procedure than in outside-in procedures [11]. Nevertheless, this database needs to be interpreted cautiously, as no incidence rate can be derived from them, and reporting bias cannot be accounted for. A non-randomised prospective study by Debodinance [13] compared the outside-in (Monarc) to the inside-out (TVT-O) procedure. No difference in thigh pain could be detected between both groups, with pain being reported in 8% of patients in both groups. The 1-year follow-up data by Waltregny et al. [12] do not specify the number of patients who reported postoperative pain in the thighs. Of note, among patients included in this study, none complained of persistent pain.

Conclusions

Study of the anatomical path of the inside-out transobturator technique in this article confirmed the previously reported observation that the TVT-O trajectory is susceptible to greater variation than originally described. The trajectory will be too cranial and too lateral when the hips are not hyperflexed. This situation may clinically present itself in cases of hip prostheses, arthrosis, obesity and inexperience with the procedure. A similar situation may occur when the metal shield to guide the needle away from the bladder is introduced at a distance greater than 1 cm away from the urethral meatus or too deep behind the ischiopubic ramus. The needle should only be allowed to just perforate the obturator membrane. Bringing the handle to a vertical position as rapidly as technically possible will create a more horizontal track, which is preferable.

On the basis of our findings and those of others [10], we feel justified to caution surgeons against an excessive feeling of safety especially when applying the TVT-O technique to certain patients. We wish to stress that minor deviations from the operative procedure, as described by de Leval [6], will result in significant deviations of the needle's peripheral course and that strict adherence to the standard procedure, is therefore extremely important. We recommend paying attention to flexion in the hips during positioning of the patient, incising the vagina at 1 cm from the urethral meatus, minimising the depth of insertion of the needle behind the ischiopubic ramus and the immediate vertical placement of the needle's handle during its angulation.

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